ANNALS of Clinical and Translational Neurology
Open Access
AMERICAN NEUROLOGICAL ASSOCIATION

RESEARCH ARTICLE

Impact of lipid profiles on parenchymal hemorrhage and early outcome after mechanical thrombectomy

Jie Li[1,2,3,*], Ling Long[4,*], Heng Zhang[1,2,3,*], Junliu Zhang[1,2,3,*], Adilijiang Abulimiti[2], Nuerbiya Abulajiang[2], Qingbo Lu[2], Wei Yan[2], Thanh N. Nguyen[5] & Xiaodong Cai[1,3]

[1]Department of Neurology, The Sixth Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China
[2]Department of Neurology, The First People's Hospital of Kashi Prefecture, Kashi, China
[3]Biomedical Innovation Center, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China
[4]Department of Neurology, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China
[5]Department of Neurology, Radiology, Boston Medical Center, Boston University Chobanian and Avedisian School of Medicine, Boston, Massachusetts, USA

Correspondence
Xiaodong Cai, Department of Neurology, The Sixth Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China. Tel: +86 13416183292; Fax: 020-38254072; E-mail: caixd3@mail.sysu.edu.cn

Thanh N. Nguyen, Department of Neurology, Radiology, Boston Medical Center, Boston University Chobanian and Avedisian School of Medicine, Boston, MA, USA. Tel: 617 638 8000; Fax: 6176385354; E-mail: thanh.nguyen@bmc.org

Wei Yan and Qingbo Lu, Department of Neurology, The First People's Hospital of Kashi Prefecture, Kashi, China. Tel: +86 135 6567 2266; Fax: 09982962654; E-mail: ywksxj@163.com (W. Y.) and Tel: +86 132 0118 6636; Fax: 09982962654; E-mail: luqingbo1029@163.com (Q. L.)

Received: 22 March 2023; Revised: 12 June 2023; Accepted: 13 July 2023

Annals of Clinical and Translational Neurology **2023; 10(10): 1714–1724**

doi: 10.1002/acn3.51861

*These authors contributed equally to this work.

Abstract

Objective: We aimed to investigate the association of lipid parameters with parenchymal hemorrhage (PH) and early neurological improvement (ENI) after mechanical thrombectomy (MT) in stroke patients. **Methods**: We retrospectively analyzed consecutive patients who underwent MT between January 2019 and February 2022 at a tertiary stroke center. PH was diagnosed and classified as PH-1 and PH-2 according to the European Cooperative Acute Stroke Study definition. ENI was defined as a decrease in the National Institutes of Health Stroke Scale (NIHSS) score by ≥8 or an NIHSS score of ≤1 at 24 h after MT. **Results**: Among 155 patients, PH occurred in 41 (26.5%) patients, and 34 (21.9%) patients achieved ENI. In multivariate analysis, lower triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C) value (OR = 0.51; 95% CI 0.30–0.89; $p = 0.017$) and higher HDL-C level (OR = 5.83; 95% CI 1.26–26.99; $p = 0.024$) were independently associated with PH. The combination of TG <0.77 mmol/L and HDL-C ≥ 0.85 mmol/L was the strongest predictor of PH (OR = 10.73; 95% CI 2.89–39.87; $p < 0.001$). A low HDL-C level was an independent predictor of ENI (OR 0.13; 95% CI 0.02–0.95; $p = 0.045$), and PH partially accounts for the failure of ENI in patients with higher HDL-C levels (estimate: −0.05; 95% CI: −0.11 to −0.01; $p = 0.016$). **Interpretation**: The combination of lower TG level and higher HDL-C level can predict PH after MT. Postprocedural PH partially accounts for the failure of ENI in patients with higher HDL-C levels. Further studies into the pathophysiological mechanisms underlying this observation are of interest.

Introduction

Mechanical thrombectomy (MT) has been proven to be effective for patients with acute ischemic stroke (AIS) caused by large-vessel occlusion.[1] With the DAWN and DEFUSE3 trials extending the time window for MT to 24 h, more patients with AIS are eligible and benefit from MT.[2,3] However, more than 50% of patients still have unfavorable outcomes after successful recanalization.[4] Early neurological improvement (ENI) as measured by the change in the National Institutes of Health Stroke Scale (NIHSS) score is a valid parameter of the effect of MT and is a predictor of favorable long-term clinical outcomes.[5] In addition, hemorrhagic transformation

(HT), especially parenchymal hemorrhage (PH), is the most severe complication of MT and is associated with high mortality and disability.[6] PH-2 which represents more extended parenchymal hematoma is the only subtype of HT that was found to be associated with early deterioration and of 3-month mortality after intravenous thrombolysis.[7] Early identification of factors associated with PH and ENI may inform potential targets for periprocedural medical management.

Hyperlipidemia is an important risk factor for cardiovascular disease.[8] Clinical studies have focused on the relationship of serum lipid markers with HT and clinical outcomes after an acute ischemic event. However, these studies yielded conflicting results. Several studies reported lower low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), total cholesterol (TC), and nonhigh-density lipoprotein cholesterol (HDL-C) levels indicating an increased risk of HT after AIS.[9–12] However, others reported that LDL-C, TC, TG, and HDL-C levels did not correlate with HT after AIS.[13–15] Moreover, several studies found that low TG and TG/HDL-C values were independently associated with poor outcomes after AIS.[8,10,16] However, the association of lipid profiles with PH and ENI remains unexplored in patients with AIS who are treated with MT. In addition, PH-2 as the most severe subtype of HT in the radiological classification scheme has rarely been distinguished from hemorrhagic infarction (HI) and PH-1 in previous studies.

In this study, we aimed to investigate the impact of serum lipid profiles on PH, PH-2, and ENI in patients with AIS who are treated by MT. Given the observations of some of these prior AIS reports, we hypothesized that patients with low LDL-C, TG, and high HDL-C levels may have a higher likelihood of HT and a lower likelihood of ENI.

Methods

Patient population

We retrospectively investigated consecutive patients with AIS who underwent MT at our institution between January 2019 and February 2022. The study was approved by the ethics committee of The First People's Hospital of Kashi Prefecture. Patient informed consent was waived due to the retrospective study design.

Inclusion criteria were: (1) age ≥ 18 years; (2) admitted within 24h of symptom onset; (3) large-vessel occlusion demonstrated by magnetic resonance or computed tomography (CT) angiography; (4) treated by MT with or without intravenous thrombolysis; (5) follow-up CT performed at 24 h after MT to evaluate HT; (6) measurement of fasting blood lipid levels within 24 hours of admission. Exclusion criteria were: (1) presence of intracranial hemorrhage before MT, (2) hepatitis, cirrhosis, liver cancer, coagulation dysfunction, or thrombocytopenia, and (3) no clinical or imaging information or no results for blood lipid levels.

Endovascular treatment procedure

Patients admitted within 4.5 h of symptom onset were treated with intravenous recombinant tissue plasminogen activator if they had no contraindications. MT was initiated directly if there were contraindications to thrombolysis or in the presence of a significant thrombus burden. Solitaire or Solitaire AB stent retriever thrombectomy was performed as the first-line thrombectomy technique. If recanalization was unsuccessful (modified Thrombolysis in Cerebral Infarction score < 2b), balloon angioplasty or stent implantation was performed.

Collection of data

Baseline characteristics included patient demographics, vascular risk factors, medical history, NIHSS score on admission, baseline ASPECTS (Alberta Stroke Program Early Computed Tomography Score), procedure-related data, and stroke etiology identified by the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification system. Fasting blood lipid levels were measured using an automated biochemistry analyzer within 24 h of admission. Serum TC and TG levels were measured by enzyme assays (CHOP-PAP and GPO-PAP). HDL-C and LDL-C levels were measured using an enzymatic clearance assay (CAT method).

Outcomes

HT was diagnosed and classified as HI or PH following the European Cooperative Acute Stroke Study III[17] based on 24 h CT. PH-1 was defined as the presence of hemorrhage in ≤30% of the infarcted area with some space-occupying effect and PH-2 as hemorrhage in >30% of the infarcted area with a substantial space-occupying effect. Symptomatic intracranial hemorrhagic (sICH) was diagnosed according to the Heidelberg bleeding classification.[17] Patients were divided into PH and non-PH, PH-2 and non-PH-2 groups. The non-PH group represented patients with no HT or cases with only the HI subtype, the non-PH-2 group represented patients with no HT or cases with HI or PH-1 subtype. The HT outcomes were adjudicated by two neuroradiologists with more than 5-year experience who were blinded to the patient's clinical condition. Disease severity was assessed by the NIHSS score 24 hours after MT and at discharge. ENI was defined as a decrease in the NIHSS score by ≥8 points or an NIHSS score of ≤1 at 24 h after MT.[18,19]

Statistical analysis

The baseline patient characteristics and outcome parameters are shown as the mean (standard deviation) or as the median with interquartile range (IQR) for continuous variables, and as the frequency or proportion for categorical variables. Differences in characteristics between the PH and non-PH, PH-2 and non-PH-2, ENI and non-ENI groups were compared using the independent-sample *t*-test or Mann–Whitney U test for continuous variables and the chi-squared or Fisher's exact test for categorical variables. Because some patients with missing data were excluded, we compared the characteristics between participants with complete data and those with incomplete data in the supplemental materials (Table S1).

The association between lipid parameters and PH and ENI after MT was assessed in binary logistic regression models. Variables with a p-value <0.1 in univariate analysis and clinically significant variables were entered into the multivariate analysis. Receiver-operating characteristic (ROC) curve analyses were used to determine the optimal TG, HDL-C, and TG/HDL-C cutoff values that identified PH. The optimal cutoffs were determined at the maximal Youden index. Based on these thresholds, we converted TG and HDL-C to binary variables. Next, we used binary logistic regression models to assess the association of the combination of binary TG and HDL-C (TG-HDL-C) with PH. We then used ROC curve analysis to assess the TG-HDL-C combination's ability to identify PH.

All the above statistical analyses were performed using IBM SPSS statistics version 26.0 software (IBM Corp., Armonk, NY, USA). All significant tests were two-sided and a p-value <0.05 was considered statistically significant.

Mediation analyses were performed to determine whether PH mediated the relation between HDL-C level and ENI by using mediation Packages in R, version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). The causal mediation analyses were conducted using a nonparametric bootstrap approach, which can automatically judge the model type and calculate the estimate of the average causal mediation effect (ACME), average direct effect (ADE), total effect, and proportion. The number of bootstrap samples in each analysis was set to 1000 to obtain a more stable estimate of the effect.

Results

Baseline characteristics and treatment outcomes of the study population

Initially, 183 patients with acute large-vessel occlusion who underwent MT were enrolled. After excluding 23 patients without lipid level data, 3 without follow-up CT, and 2 with an equivocal NIHSS score at baseline, data for 155 patients were included in the study (Fig. S1). There 54.8% (85/155) of patients were men. The mean patient age was 54.9 ± 13.8 years. The median baseline NIHSS and ASPECTS scores were 12 (IQR 9–16) and 9 (IQR 8–10), respectively. A total of 48 (31.0%) patients received intravenous thrombolysis. In total, 26.5% (41/155) were diagnosed with PH, 14.8% (23/155) were diagnosed with PH-2, and 34 (21.9%) achieved ENI at 24 h after MT (Table S1).

Factors associated with parenchymal hemorrhage after mechanical thrombectomy

Compared with the non-PH group, patients with PH had a lower body mass index (BMI; 23.5 vs 25.1, $p = 0.046$), a higher proportion with tandem occlusion (31.7% vs 14.9%, $p = 0.020$), a lower TG level (1.03 mmol/L vs 1.25 mmol/L, $p = 0.030$), a lower TG/HDL-C value (0.98 vs 1.47, $p = 0.003$), and a higher HDL-C level (1.03 mmol/L vs 0.88 mmol/L, $p = 0.010$). (Table 1). After adjustment for age, BMI, baseline NIHSS score, baseline ASPECTS, tandem occlusion, and bridging thrombolysis, multivariate logistic regression analysis showed that the HDL-C level (adjusted odds ratio [aOR] 5.83; 95% CI 1.26–26.99; $p = 0.024$) and TG/HDL-C value (aOR 0.51; 95% CI 0.30–0.89; $p = 0.017$) were independently associated with PH (Table 3, Table S4).

Patients with PH-2 had a lower BMI (24.2 vs 25.0, $p = 0.040$), a longer procedure time (170 min vs 139 min, $p = 0.018$), higher rate with general anesthesia (39.1% vs 18.9%, $p = 0.031$) and tandem occlusion (34.8% vs 16.7%, $p = 0.042$), a higher HDL-C level (1.06 mmol/L vs 0.89 mmol/L, $p = 0.003$), lower TC/HDL-C (3.81 vs 4.22, $p = 0.028$), TG/HDL-C (0.98 vs 1.40, $p = 0.013$), and LDL-C/HDL-C (2.18 vs 2.92, $p = 0.042$) values than those without PH-2. (Table S2). After adjustment for age, BMI, baseline NIHSS score, baseline ASPECTS score, tandem occlusion, procedure time, requirement for general anesthesia, and bridging thrombolysis, the HDL-C level (aOR 11.38; 95% CI 1.67–77.45; $p = 0.013$) and TG/HDL-C value (aOR 0.44; 95% CI 0.19–0.99; $p = 0.047$) were independently associated with PH-2 (Table 3, Table S5).

Ability of TG, HDL-C, TG/HDL-C, and TG-HDL-C to predict parenchymal hemorrhage

Figure 1 shows the ROC curves for the ability of lipid parameters to correlate with PH and PH-2. For PH, the optimal thresholds for the ability of TG and HDL-C to

Table 1. Demographic and clinical characteristics of participants in PH and non-PH groups.

Variable	PH (n = 41)	Non-PH (n = 114)	p-Value
Age, mean ± SD, years	56.0 ± 14.6	54.5 ± 13.6	0.537
Male, *n* (%)	22 (53.7)	63 (55.3)	0.859
BMI, median (IQR), kg/m^2	23.5 (21.8–25.7)	25.1 (23.4–27.4)	0.046
Risk factors			
Smoking, *n* (%)	7 (17.1)	31 (27.2)	0.196
Diabetes mellitus, *n* (%)	6 (14.6)	22 (19.3)	0.506
Hypertension, *n* (%)	15 (36.6)	45 (39.5)	0.745
Atrial fibrillation, *n* (%)	12 (29.3)	23 (20.2)	0.232
History of stroke/TIA, *n* (%)	4 (9.8)	12 (10.5)	0.889
Prior anticoagulant/antiplatelet drug use, *n* (%)	7 (17.1)	27 (23.7)	0.380
Clinical variables			
Baseline NIHSS score, median (IQR)	13 (11–17)	12 (8–16)	0.228
Baseline ASPECTS, median (IQR)	9 (8–10)	9 (8–10)	0.563
Onset-to-puncture time, median (IQR), min	412 (319–728)	478 (311–832)	0.362
Procedure duration, min	145 (113–222)	139 (100–183)	0.249
SBP after MT, median (IQR), mmHg	126 (117–142)	130 (114–150)	0.568
DBP after MT, median (IQR), mmHg	75 (66–87)	80 (69–90)	0.120
Bridging thrombolysis, *n* (%)	14 (34.1)	34 (29.8)	0.608
TOAST classification			
Cardioembolism, *n* (%)	18 (43.9)	43 (37.7)	0.487
Large arterial atherosclerosis, *n* (%)	18 (43.9)	61 (53.5)	0.291
Undetermined/others, *n* (%)	5 (12.2)	10 (8.8)	0.525
General anesthesia, *n* (%)	12 (29.3)	22 (19.3)	0.186
Stent retriever passes, median (IQR)	2 (1–2)	2 (1–3)	0.551
mTICI score 2b or 3, *n* (%)	38 (92.7)	94 (82.5)	0.132
Tandem occlusion, *n* (%)	13 (31.7)	17 (14.9)	0.020
Rescue therapy, *n* (%)	7 (17.1)	22 (19.3)	0.754
Laboratory data			
Serum glucose, median (IQR), mmol/L	6.4 (5.6–8.7)	6.5 (5.7–8.2)	0.826
Uric Acid, mean ± SD, μmol/L	269.6 ± 80.7	294.6 ± 101.0	0.211
TC, median (IQR), mmol/L	3.85 (3.18–4.80)	4.00 (3.16–4.54)	0.849
TG, median (IQR), mmol/L	1.03 (0.74–1.65)	1.25 (0.92–1.72)	0.030
HDL-C, median (IQR), mmol/L	1.03 (0.87–1.21)	0.88 (0.77–1.06)	0.010
LDL-C, median (IQR), mmol/L	2.51 (2.02–3.23)	2.55 (2.02–3.28)	0.692
TC/HDL-C, median (IQR)	3.94 (3.31–4.61)	4.24 (3.48–5.09)	0.087
TG/HDL-C, median (IQR)	0.98 (0.75–1.68)	1.47 (0.99–2.17)	0.003
LDL-C/HDL-C, median (IQR)	2.63 (2.07–3.24)	2.92 (2.17–3.52)	0.241

ASPECTS, Alberta Stroke Program Early Computed Tomography score; BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; mTICI, modified thrombolysis in cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; PH, parenchymal hemorrhage; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

predict PH were 0.77 and 0.85 mmol/L, respectively. The predictive ability of the combined binary variates TG and HDL-C (TG-HDL-C: AUC 0.704, 95% CI 0.612–0.796, $p < 0.001$) was significantly better than that of HDL-C (AUC 0.635, 95% CI 0.540–0.731, $p = 0.010$) and TG/HDL-C (AUC 0.659, 95% CI 0.563–0.754, $p = 0.003$). For PH-2, the optimal cutoff points for TG and HDL-C were 0.80 and 0.87 mmol/L, respectively. The predictive ability of TG-HDL-C (AUC 0.766, 95% CI 0.668–0.863, $p < 0.001$) was also superior to that of HDL-C (AUC 0.695, 95% CI 0.591–0.799, $p = 0.003$) and TG/HDL-C (AUC 0.662, 95% CI 0.544–0.780, $p = 0.013$) (Table S6).

Figure 2 and Table S7 show the ability of the combination of the binary variates TG and HDL-C to predict PH and PH-2. When TG was set at ≥0.77 mmol/L and HDL-C at <0.85 mmol/L, which predicted the lowest risk of PH as the reference, the combination of TG <0.77 mmol/L and HDL-C ≥ 0.85 mmol/L had the best ability to predict PH (aOR 10.73; 95% CI 2.89–39.87; $p < 0.001$). Setting TG at ≥0.80 mmol/L and HDL-C at <0.87 mmol/L as the reference, the combination of TG <0.80 mmol/L and HDL-C ≥ 0.87 mmol/L was the strongest predictor of PH-2 (aOR 52.29; 95% CI 4.86–562.60, $p = 0.001$).

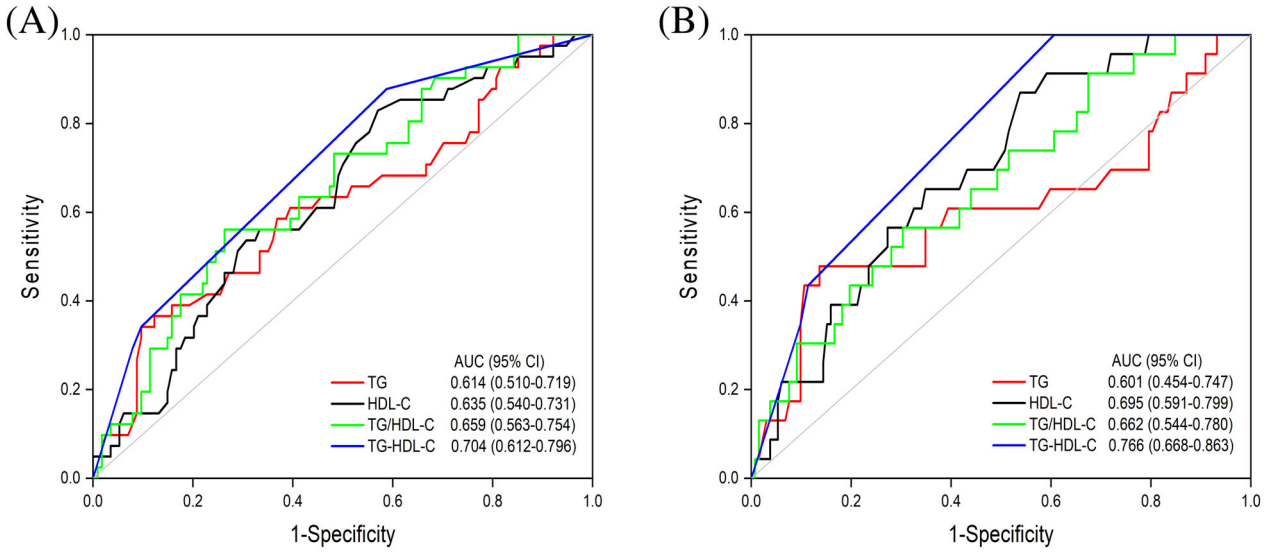

Figure 1. Receiver-operating characteristic curve analysis showing the predictive power of TG, HDL-C, TG/HDL-C, and TG-HDL-C (combined binary variates TG and HDL-C) for PH (A) and PH-2 (B) in AIS patients after MT. The predictive ability of TG-HDL-C for PH and PH-2 was significantly better than that of TG, HDL-C, and TG/HDL-C. AIS, acute ischemic stroke; HDL-C, high-density lipoprotein cholesterol; MT, mechanical thrombectomy; PH, parenchymal hemorrhage; TG, triglyceride.

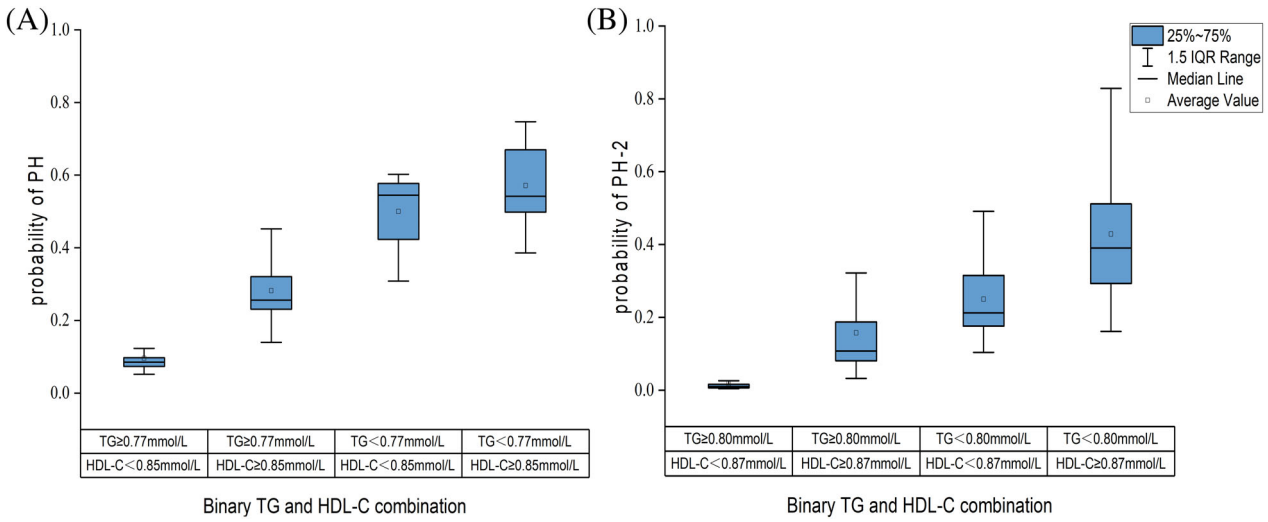

Figure 2. A combination of binary variates TG and HDL-C for predicting PH (A) and PH-2 (B) in AIS patients who underwent MT. The combination of TG <0.77 mmol/L and HDL-C ≥ 0.85 mmol/L was the strongest predictor of PH, and the combination of TG <0.80 mmol/L and HDL-C ≥ 0.87 mmol/L was the strongest predictor of PH-2. AIS, acute ischemic stroke; HDL-C, high-density lipoprotein cholesterol; MT, mechanical thrombectomy; PH, parenchymal hemorrhage; TG, triglyceride.

Factors associated with early neurological improvement after mechanical thrombectomy

Compared with patients without ENI, those who developed ENI had a higher baseline ASPECTS (9.5 vs 9.0, $p = 0.037$), a shorter onset-to-groin puncture time (401 vs 548, $p = 0.022$), and procedure duration time (118 vs 150, $p = 0.004$), a lower PH rate (8.8% vs 31.4%, $p = 0.008$), and a lower level of HDL-C (0.85 mmol/L vs 0.92 mmol/L, $p = 0.035$) (Table 2, Table S3). The multivariate logistic regression analyses showed that baseline ASPCTS per 1-point increment (OR 1.48; 95% CI 1.01–2.91; $p = 0.046$), procedure duration per 10 min

Table 2. Demographic and clinical characteristics of participants in ENI and fENI groups.

Variable	ENI (n = 34)	fENI (n = 121)	p-Value
Age, mean ± SD, years	51.8 ± 15.4	55.8 ± 13.3	0.138
Male, *n* (%)	18 (52.9)	67 (55.4)	0.801
BMI, median (IQR), kg/m^2	25.3 ± 3.4	25.0 ± 3.4	0.590
Risk factors			
Smoking, *n* (%)	8 (23.5)	30 (24.8)	0.880
Diabetes mellitus, *n* (%)	4 (11.8)	24 (19.8)	0.326
Hypertension, *n* (%)	13 (38.2)	47 (38.8)	0.949
Atrial fibrillation, *n* (%)	5 (14.7)	30 (24.8)	0.241
History of stroke/TIA, *n* (%)	4 (11.8)	12 (9.9)	0.753
Prior anticoagulant/antiplatelet drug use, *n* (%)	11 (32.4)	23 (18.2)	0.097
Clinical variables			
Baseline NIHSS score, median (IQR)	13.0 (9.0–17.0)	12.0 (9.0–15.5)	0.404
Baseline ASPECTS, median (IQR)	9.5 (8.8–10.0)	9.0 (8.0–10.0)	0.037
Onset-to-puncture time, median (IQR), min	401 (243–558)	548 (329–834)	0.022
Procedure duration, min	118 (90–153)	150 (111–211)	0.004
SBP after MT, median (IQR), mmHg	131 (107–143)	129 (118–151)	0.164
DBP after MT, median (IQR), mmHg	78 (68–87)	79 (69–90)	0.666
Bridging thrombolysis, *n* (%)	11 (32.4)	37 (30.6)	0.843
TOAST classification			
Cardioembolism, *n* (%)	17 (50.0)	44 (36.4)	0.150
Large arterial atherosclerosis, *n* (%)	13 (38.2)	66 (54.5)	0.093
Undetermined/others, *n* (%)	4 (11.8)	11 (9.1)	0.743
General anesthesia, *n* (%)	6 (17.6)	28 (23.1)	0.494
Stent retriever Passes, median (IQR)	1.0 (1.0–2.0)	2.0 (1.0–3.0)	0.551
mTICI score 2b or 3, *n* (%)	32 (94.1)	100 (82.6)	0.096
Tandem occlusion, *n* (%)	4 (11.8)	26 (21.5)	0.325
Rescue therapy, *n* (%)	4 (11.8)	25 (20.7)	0.240
Laboratory data			
Serum glucose, median (IQR), mmol/L	6.0 (5.3–7.7)	6.5 (5.7–8.6)	0.104
Uric acid, mean ± SD, μmol/L	289.7 ± 103.6	286.5 ± 95.4	0.866
TC, median (IQR), mmol/L	3.54 (3.05–4.20)	4.01 (3.21–4.72)	0.113
TG, median (IQR), mmol/L	1.15 (0.96–1.60)	1.22 (0.83–1.75)	0.589
HDL-C, median (IQR), mmol/L	0.85 (0.70–0.97)	0.92 (0.81–1.13)	0.035
LDL-C, median (IQR), mmol/L	2.36 (2.04–2.93)	2.59 (1.99–3.30)	0.327
TC/HDL-C, median (IQR)	4.38 (3.36–5.28)	4.13 (3.43–4.89)	0.568
TG/HDL-C, median (IQR)	1.51 (1.00–2.20)	1.31 (0.86–1.87)	0.143
LDL-C/HDL-C, median (IQR)	3.04 (2.05–4.00)	2.75 (2.09–3.44)	0.480

ASPECTS, Alberta Stroke Program Early Computed Tomography score; BMI, body mass index; DBP, diastolic blood pressure; fENI, failure of early neurological improvement; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; mTICI, modified thrombolysis in cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; TC, total cholesterol; TG, triglyceride.

increment (OR 0.92; 95% CI 0.85–0.99; p = 0.020), HDL-C level per 1.0 mmol/L increment (OR 0.13; 95% CI 0.02–0.95; p = 0.045), and HDL-C <0.81 mmol/L (OR 3.50; 95% CI 1.41–8.74; p = 0.007) were independently associated with ENI. (Table 4).

Figure 3 shows the results of the causal mediation analyses. The direct effect (estimate: −0.36; 95% CI: −0.70 to −0.01; p = 0.048) and total effect (estimate: −0.41; 95% CI: −0.73 to −0.04; p = 0.032) were significantly present between HDL-C levels and ENI. The indirect effect of the PH (estimate: −0.05; 95% CI: −0.11 to −0.01; p = 0.016) was significant for the relation between HDL-C and ENI, and 11.5% of the total effect contributed to mediation by the presence of PH after adjusting for tandem occlusions, procedure duration, NIHSS score, and ASPECTS.

Discussion

The findings of this study suggest that a low TG/HDL-C value and a high HDL-C level are independently associated with an increased PH or PH-2 risk after MT in patients with AIS. Moreover, PH and PH-2 were better predicted by a combination of TG and HDL-C as binary

Table 3. Univariate and multivariate logistic regression analysis of the association between lipid parameters and PH and PH-2.

	PH				PH-2			
	Unadjusted OR (95% CI)	*p*-Value	Adjusted OR (95% CI)[1]	*p*-Value	Unadjusted OR (95% CI)	*p*-Value	Adjusted OR (95% CI)[2]	*p*-Value
TG, mmol/L	0.54 (0.30–0.997)	0.049	0.58 (0.31–1.08)	0.088	0.66 (0.33–1.33)	0.242	0.69 (0.32–1.47)	0.332
HDL-C, mmol/L	6.28 (1.47–26.81)	0.013	5.83 (1.26–26.99)	0.024	11.75 (2.05–67.37)	0.006	11.38 (1.67–77.45)	0.013
TG/HDL-C	0.48 (0.28–0.83)	0.008	0.51 (0.30–0.89)	0.017	0.44 (0.21–0.92)	0.029	0.44 (0.19–0.99)	0.047
TC/HDL-C	0.73 (0.53–0.995)	0.047	0.77 (0.55–1.07)	0.122	0.61 (0.39–0.96)	0.031	0.65 (0.40–1.05)	0.079
LDL-C/HDL-C	0.75 (0.53–1.07)	0.113	0.80 (0.55–1.17)	0.264	0.59 (0.36–0.97)	0.039	0.63 (0.37–1.09)	0.095

HDL-C, high-density lipoprotein cholesterol; LDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.
[1]Adjusted for age, BMI, baseline NIHSS score, baseline ASPECTS score, tandem occlusion, and bridging thrombolysis.
[2]Adjusted for age, BMI, baseline NIHSS score, baseline ASPECTS score, tandem occlusion, procedure time, requirement for general anesthesia, and bridging thrombolysis.

Table 4. Independent predictors of ENI in univariate and multivariate logistic regression analysis.

	Unadjusted OR (95% CI)	*p*-Value	Model1 OR (95% CI)	*p*-Value	Model2 OR (95% CI)	*p*-Value
Baseline ASPECTS, per 1-point increase	1.50 (1.07–2.12)	0.020	1.48 (1.01–2.19)	0.046	1.49 (1.004–2.21)	0.047
OTP, per 10 min increase	0.98 (0.97–0.996)	0.014	0.99 (0.98–1.003)	0.131	0.99 (0.97–1.003)	0.130
Procedure duration, per 10 min increase	0.90 (0.84–0.97)	0.004	0.92 (0.85–0.99)	0.020	0.90 (0.84–0.98)	0.010
Large arterial atherosclerosis	1.94 (0.89–4.22)	0.096	0.94 (0.38–2.34)	0.891	0.85 (0.34–2.17)	0.741
mTICI score ≥ 2b	0.30 (0.07–1.34)	0.114	0.37 (0.07–1.86)	0.229	0.32 (0.06–1.67)	0.176
HDL-C per 1 mmol/L increase	0.13 (0.02–0.78)	0.025	0.13 (0.02–0.95)	0.045	–	–
HDL-C < 0.81 mmol/L	2.58 (1.17–5.67)	0.018	–	–	3.50 (1.41–8.74)	0.007

ASPECTS, Alberta Stroke Program Early Computed Tomography score; HDL-C, high-density lipoprotein cholesterol; mTICI, modified thrombolysis in cerebral Infarction; OTP, Onset-to-groin puncture time; SBP, systolic blood pressure.

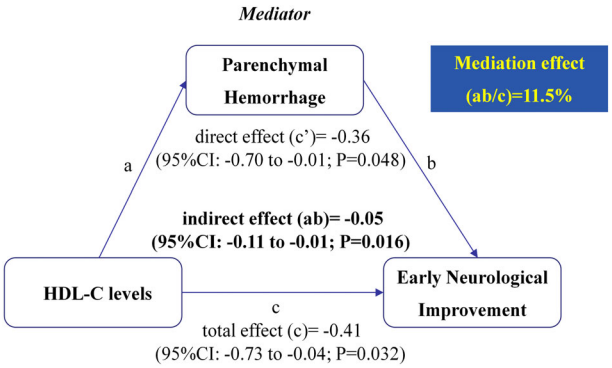

Figure 3. Causal mediation analysis is shown for the presence of parenchymal hemorrhage as a mediator in the relation between HDL-C levels and early neurological improvement. The mediation effect is the indirect effect expressed as a percentage of the total effect. HDL-C, high-density lipoprotein cholesterol.

variates than by TG, HDL-C, or TG/HDL-C. In addition, a high level of HDL-C was associated with decreased probability of ENI, and postprocedural PH was partially responsible for the failure of ENI in patients with higher HDL-C levels.

HT is the most severe complication after MT and is associated with an increased risk of mortality and poor functional outcomes. The European Cooperative Acute Stroke Study III categorizes HT as HI or PH, the latter of which represents a more serious category. Previous studies found that PH, but not HI, was independently associated with an increased risk of death and disability.[20,21]

In previous studies, the HT rate after MT ranged from 29.4% to 42.6% and the sICH rate ranged from 6.3% to 12.4%.[22–25] In our study, the HT rate was 41.9% and the sICH rate was 10.3%, in line with the results of previous studies. An observational study reported a PH rate of 25.7%,[26] which is close to our rate of 26.5%. In our study, the LDL-C/HDL-C and TC/HDL-C values were significantly lower in the PH-2 group than in the non-PH-2 group, which is concordant with previous studies.[9,27] We also found a lower BMI and higher tandem occlusion rates in our PH and PH-2 groups, and a higher rate of patients with PH-2 requiring general anesthesia.

One study found that an elevated serum HDL-C level and decreased TG level were associated with an increased risk of lobar cerebral microbleeds in older patients.[28] A

recent study identified that a high HDL-C level was a risk factor for HT.[29] Deng et al. demonstrated that a low TG/HDL-C value increased the risk of HT after AIS attributed to LAA.[10] Luo et al. reported that a low TG/HDL-C value was associated with an increased risk of HT in patients with AIS who received intravenous thrombolysis.[27] Altogether, the above-mentioned studies suggest that a lower TG level and a higher HDL-C level can predict HT, which aligns with our findings. However, those studies only included small numbers of patients with MT and did not classify HT into HI and PH, therefore, they did not explore the association of TG and HDL-C levels with different levels of PH after MT. In the present study, both HDL-C and TG/HDL-C were significantly correlated with the PH and PH-2 risk. Each 1.0-mmol/L increment in HDL-C indicated a 5.8-fold increase in the probability of PH and an 11.4-fold increase in PH-2, and each 1.0 increment in the TG/HDL-C value indicated respective increases in the risk of PH and PH-2 by 0.51-fold and 0.44-fold.

The mechanisms by which TG and HDL-C levels are associated with PH remain unclear. There are several possible explanations for this phenomenon. TG and cholesterol are essential structural elements that play an important role in maintaining cell membrane homeostasis.[30] Low TG and cholesterol levels are thought to cause smooth muscle cell degradation, endothelial damage, and arterial fragility, which can lead to leakage and vessel wall rupture.[31,32] Furthermore, a high TG level shows a positive correlation with coagulation factor VII and fibrinogen, and a negative correlation with plasminogen activator inhibitor, suggesting that a hemorrhagic tendency exists at low TG levels.[33] HDL-C exhibits various actions according to the stroke subtype. A high HDL-C level protects against ischemic stroke but increases the intracranial hemorrhage risk.[34] HDL can transport excess cholesterol from the peripheral tissues to the liver,[35] resulting in increased cholesterol efflux from the blood–brain barrier, which may weaken the vascular endothelium. HDL-C also prevents platelet hyperreactivity, suppresses the coagulation cascade, and stimulates fibrinolysis, which inhibits thrombosis.[36] The combination of a low TG level and high HDL-C level reflects a vulnerable blood–brain barrier, thereby serving as a potential predictor of an increased risk of PH after MT.

We also derived optimal TG and HDL-C cutoff points for predicting PH and PH-2. We found that a binary TG-HDL-C combination based on these cutoff points had the best predictive value. Patients with a TG level <0.77 mmol/L and an HDL-C level ≥ 0.85 mmol/L were at the highest risk of PH and those with a TG level <0.80 mmol/L and an HDL-C level ≥ 0.87 mmol/L were at the highest risk of PH-2.

Previous studies have suggested that ENI is a predictor of long-term outcomes after MT for AIS.[5] Favorable cerebral collateral perfusion,[37] ASPECTS region, higher premorbid MRS, end-stage renal failure, high glucose level on admission, absence of bridging thrombolysis, general anesthesia, and a longer therapy interval[38] have been reported to be associated with ENI after MT. We explored the relationship between serum lipid profiles and ENI in this study and found that each 1.0-mmol/L increment in HDL-C indicated a 0.13-fold increase in the likelihood of ENI. These findings are partly in line with a study by Deng et al., which reported that a low TG/HDL-C value was associated with a poor outcome and high mortality after AIS,[16,39] and another study that demonstrated elevated non-HDL-C level was an indicator of good functional outcomes after intracerebral hemorrhage.[40] Our data demonstrated that postprocedural PH was an important mediator of the failure of ENI in patients with higher HDL-C levels. The mechanism by which HDL-C levels directly affect ENI remains uncertain. Previous studies found that cholesterol may reduce oxidative damage in phospholipid membranes, improve the tolerance to anoxic damage during reperfusion,[41,42] promote axonal regeneration and synapse development at the acute phase of ischemic stroke.[43] Higher serum levels of HDL-C were associated with increased cholesterol efflux from infarcted tissue and decreased cellular cholesterol content, thereby weakening the protective effect of cholesterol, and potentially increasing the risk of failure of ENI after MT.

To our knowledge, the relationship between serum lipid parameters and PH or ENI after MT has not been reported. This study identified that a TG-HDL-C combination can predict PH and PH-2, and HDL-C levels are associated with ENI after MT. TG and HDL-C are simple, inexpensive biomarkers that are readily available in clinical practice. Early measurements of TG and HDL-C levels are helpful for the identification of patients at risk of PH and failure of ENI, for those patients at high risk of PH, aggressive periprocedural antiplatelet therapy (dual antiplatelet therapy with or without tirofiban) should be prescribed with caution. Our findings may help develop optimal periprocedural antithrombotic strategies and provide a novel target to improve procedural safety and clinical outcomes of mechanical thrombectomy.

Limitations

This study has some limitations. First, it had a retrospective single-center design and included a relatively small sample size, which may compromise the external validity of the results. Therefore, we interpret our findings with caution when generalizing to other populations. Second,

we did not obtain serial lipid profile measurements, and it is unclear whether they fluctuated during different stages of the disease. However, previous studies have reported that lipid levels remain stable within 48 hours following AIS onset and reflect patients' baseline concentrations.[44] Third, the observational nature of the research precludes ascribing a causal association between lipid parameters with PH and ENI. Finally, although we adjusted for confounding factors, the possibility of additional unrecognized confounders cannot be ruled out.

Conclusions

In this study, a low TG/HDL-C value and a high HDL-C level were independent predictors of PH and PH-2 after MT in patients with AIS. Compared with TG, HDL-C, and TG/HDL-C, the TG-HDL-C combination better predicted PH and PH-2 after MT for AIS. In addition, a low HDL-C level was an independent predictor of ENI. Post-procedural PH partially accounted for the failure of ENI in patients with higher HDL-C levels. Early measurement of lipid levels may identify patients with AIS at high risk of PH and failure of ENI. These findings may help develop tailored medical management strategies for patients at risk of PH after MT.

Acknowledgements

We thank all patients for participating in this study and for the support from The First People's Hospital of Kashi Prefecture. This research was supported by the Natural Science Foundation of Guangdong Province, China (NO. 2022A1515012191), the Rural Special Commissioner Project of Guangdong Province (NO. KTPYJ2021017), and 1010 Program of the Sixth Affiliated Hospital of Sun Yat-Sen University (NO. 1010PY [2022]-51).

Conflict of Interest

T. Nguyen reports research support from Medtronic and the Society of Vascular and Interventional Neurology.

Author Contributions

JL and XC involved in concept and design. JL, HZ, JZ, NA, AA, and QL involved in acquisition, analysis, or interpretation of data. JL and LL involved in drafting of the manuscript. LJ, LL, TNN, and XC involved in critical revision of the manuscript for important intellectual content. JL, JZ, and XC involved in statistical analysis. WY, QL, and AA involved in administrative, technical, or material support. XC and WY involved in supervision. All authors read and approved the final manuscript.

References

1. Powers W, Rabinstein A, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2019;50 (12):e344-e418.
2. Albers G, Marks M, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med. 2018;378(8):708-718.
3. Nogueira R, Jadhav A, Haussen D, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med. 2018;378(1):11-21.
4. Seker F, Qureshi MM, Möhlenbruch MA, et al. Reperfusion without functional independence in late presentation of stroke with large vessel occlusion. Stroke. 2022;53:3594-3604.
5. Kobeissi H, Ghozy S, Bilgin C, Kadirvel R, Kallmes DF. Early neurological improvement as a predictor of outcomes after endovascular thrombectomy for stroke: a systematic review and meta-analysis. J Neurointerv Surg. 2023;15:547-551.
6. Krishnan R, Mays W, Elijovich L. Complications of mechanical Thrombectomy in acute ischemic stroke. Neurology. 2021;97:S115-S125.
7. Fiorelli M, Bastianello S, von Kummer R, et al. Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European cooperative acute stroke study I (ECASS I) cohort. Stroke. 1999;30 (11):2280-2284.
8. Deng Q, Li S, Zhang H, et al. Association of serum lipids with clinical outcome in acute ischaemic stroke: a systematic review and meta-analysis. J Clin Neurosci. 2019;59:236-244.
9. Wang Y, Song Q, Cheng Y, et al. Association between non-high-density lipoprotein cholesterol and haemorrhagic transformation in patients with acute ischaemic stroke. BMC Neurol. 2020;20(1):47.
10. Deng Q, Liu Y, Zhang Y, et al. Low triglyceride to high-density lipoprotein cholesterol ratio predicts hemorrhagic transformation in large atherosclerotic infarction of acute ischemic stroke. Aging. 2019;11(5):1589-1601.
11. Kim B, Lee S, Ryu W, Kang B, Kim C, Yoon B. Low level of low-density lipoprotein cholesterol increases hemorrhagic transformation in large artery atherothrombosis but not in cardioembolism. Stroke. 2009;40(5):1627-1632.
12. Bang O, Saver J, Liebeskind D, et al. Cholesterol level and symptomatic hemorrhagic transformation after ischemic stroke thrombolysis. Neurology. 2007;68 (10):737-742.

13. Wang Y, Cheng Y, Song Q, et al. The association between monocyte to high-density lipoprotein ratio and hemorrhagic transformation in patients with acute ischemic stroke. Aging. 2020;12(3):2498-2506.
14. Tian Y, Xie Q, You J, Yang S, Zhao H, Song Y. Lower uric acid level may be associated with hemorrhagic transformation after intravenous thrombolysis. Neurol Sci. 2021;43:3113-3120.
15. Uyttenboogaart M, Koch M, Koopman K, Vroomen P, Luijckx G, De Keyser J. Lipid profile, statin use, and outcome after intravenous thrombolysis for acute ischaemic stroke. J Neurol. 2008;255(6):875-880.
16. Deng Q, Wang H, Sun C, et al. Triglyceride to high-density lipoprotein cholesterol ratio predicts worse outcomes after acute ischaemic stroke. Eur J Neurol. 2017;24(2):283-291.
17. Neuberger U, Möhlenbruch M, Herweh C, Ulfert C, Bendszus M, Pfaff J. Classification of bleeding events: comparison of ECASS III (European cooperative acute stroke study) and the new Heidelberg bleeding classification. Stroke. 2017;48(7):1983-1985.
18. Heit JJ, Mlynash M, Kemp SM, et al. Rapid neurologic improvement predicts favorable outcome 90 days after Thrombectomy in the DEFUSE 3 study. Stroke. 2019;50 (5):1172-1177.
19. Saposnik G, Di Legge S, Webster F, Hachinski V. Predictors of major neurologic improvement after thrombolysis in acute stroke. Neurology. 2005;65 (8):1169-1174.
20. Yang N, Lin M, Wang B, et al. Low level of low-density lipoprotein cholesterol is related with increased hemorrhagic transformation after acute ischemic cerebral infarction. Eur Rev Med Pharmacol Sci. 2016;20 (4):673-678.
21. Molina C, Alvarez-Sabín J, Montaner J, et al. Thrombolysis-related hemorrhagic infarction: a marker of early reperfusion, reduced infarct size, and improved outcome in patients with proximal middle cerebral artery occlusion. Stroke. 2002;33(6):1551-1556.
22. Huang K, Zha M, Gao J, Du J, Liu R, Liu X. Increased intracranial hemorrhage of mechanical thrombectomy in acute ischemic stroke patients with atrial fibrillation. J Thromb Thrombolysis. 2021;51(2):536-544.
23. Diestro JDB, Parra-Farinas C, Balas M, et al. Inflammatory biomarkers and intracranial hemorrhage after endovascular thrombectomy. Can J Neurol Sci. 2022;49:644-650.
24. Sun C, Wu C, Zhao W, et al. Glycosylated hemoglobin A1c predicts intracerebral hemorrhage with acute ischemic stroke post-mechanical Thrombectomy. J Stroke Cerebrovasc Dis. 2020;29(9):105008.
25. Pikija S, Sztriha LK, Killer-Oberpfalzer M, et al. Neutrophil to lymphocyte ratio predicts intracranial hemorrhage after endovascular thrombectomy in acute ischemic stroke. J Neuroinflammation. 2018;15(1):319.
26. Xu C, Zhou Y, Zhang R, et al. Metallic Hyperdensity sign on noncontrast CT immediately after mechanical Thrombectomy predicts parenchymal hemorrhage in patients with acute large-artery occlusion. AJNR Am J Neuroradiol. 2019;40(4):661-667.
27. Luo Y, Chen J, Yan X, et al. Association of non-Traditional Lipid Parameters with hemorrhagic transformation and clinical outcome after thrombolysis in ischemic stroke patients. Curr Neurovasc Res. 2020;17 (5):736-744.
28. Ding J, Sigurdsson S, Garcia M, et al. Risk factors associated with incident cerebral microbleeds according to location in older people: the age, gene/environment susceptibility (AGES)-Reykjavik study. JAMA Neurol. 2015;72(6):682-688.
29. Liu J, Wang Y, Jin Y, et al. Prediction of hemorrhagic transformation after ischemic stroke: development and validation study of a novel multi-biomarker model. Front Aging Neurosci. 2021;13:667934.
30. Eryürek FG, Sürmen E, Oner P, Altuğ T, Oz H. Gamma-glutamyl transpeptidase and acetylcholinesterase activities in brain capillaries of cholesterol-fed rabbits. Res Commun Chem Pathol Pharmacol. 1990;69(2):245-248.
31. Konishi M, Iso H, Komachi Y, et al. Associations of serum total cholesterol, different types of stroke, and stenosis distribution of cerebral arteries. The Akita Pathology Study. Stroke. 1993;24(7):954-964.
32. Tirschwell DL, Smith NL, Heckbert SR, Lemaitre RN, Longstreth WT Jr, Psaty BM. Association of cholesterol with stroke risk varies in stroke subtypes and patient subgroups. Neurology. 2004;63(10):1868-1875.
33. Rosenson RS, Lowe GD. Effects of lipids and lipoproteins on thrombosis and rheology. Atherosclerosis. 1998;140 (2):271-280.
34. Qie R, Liu L, Zhang D, et al. Dose-response association between high-density lipoprotein cholesterol and stroke: a systematic review and meta-analysis of prospective cohort studies. Prev Chronic Dis. 2021;18:E45.
35. Khera AV, Cuchel M, de la Llera-Moya M, et al. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. N Engl J Med. 2011;364(2):127-135.
36. van der Stoep M, Korporaal S, Van Eck M. High-density lipoprotein as a modulator of platelet and coagulation responses. Cardiovasc Res. 2014;103(3):362-371.
37. Faizy TD, Mlynash M, Kabiri R, et al. Favourable arterial, tissue-level and venous collaterals correlate with early neurological improvement after successful thrombectomy treatment of acute ischaemic stroke. J Neurol Neurosurg Psychiatry. 2022;93:701-706.
38. Weyland CS, Mokli Y, Vey JA, et al. Predictors for failure of early neurological improvement after successful

Thrombectomy in the anterior circulation. Stroke. 2021;52(4):1291-1298.
39. Deng Q, Li S, Wang H, et al. The short-term prognostic value of the triglyceride-to-high-density lipoprotein cholesterol ratio in acute ischemic stroke. Aging Dis. 2018;9(3):498-506.
40. Feng H, Wang X, Wang W, Zhao X. Association between non-high-density lipoprotein cholesterol and 3-month prognosis in patients with spontaneous intracerebral hemorrhage. Front Neurol. 2020;11:920.
41. Cui T, Wang C, Zhu Q, et al. Association between low-density cholesterol change and outcomes in acute ischemic stroke patients who underwent reperfusion therapy. BMC Neurol. 2021;21(1):360.
42. Pikija S, Sztriha LK, Killer-Oberpfalzer M, et al. Contribution of serum lipid profiles to outcome after endovascular Thrombectomy for anterior circulation ischemic stroke. Mol Neurobiol. 2019;56(6):4582-4588.
43. Goritz C, Mauch DH, Pfrieger FW. Multiple mechanisms mediate cholesterol-induced synaptogenesis in a CNS neuron. Mol Cell Neurosci. 2005;29(2):190-201.
44. Kargman D, Tuck C, Berglund L, et al. Lipid and lipoprotein levels remain stable in acute ischemic stroke: the northern Manhattan stroke study. Atherosclerosis. 1998;139(2):391-399.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1

